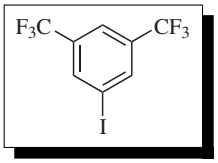
3,5-Bis(trifluoromethyl)iodobenzene



[328-73-4] $C_8H_3F_6I$ (MW 340.00)

InChI = 1/C8H3F6I/c9-7(10,11)4-1-5(8(12,13)14)3-6(15)2-4/h1-3H

InChIKey = VDPIZIZDKPFXLI-UHFFFAOYAN

(reagent used as a versatile allylation or arylation component)

Physical Data: bp 59–61 °C (10 mmHg); fp 74 °C; *d* 1.919 g cm^{-3}.

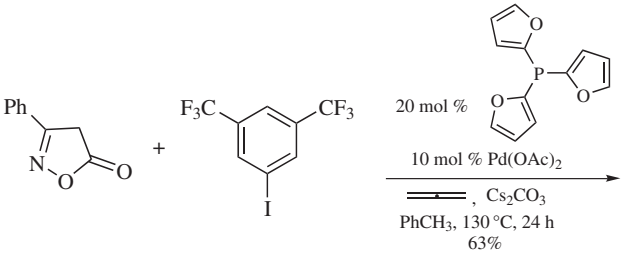
Solubility: sol DMF, acetonitrile, toluene, and most organic solvents.

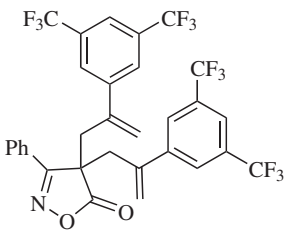
Form Supplied in: pale pink liquid; commercially available.

Purification: dried over $MgSO_4$ and fractionally distilled under vacuum.

Handling, Storage, and Precautions: air, light, and moisture sensitive; to be handled in an inert atmosphere; stored in cool, dark, and dry conditions and away from oxidizing agents.

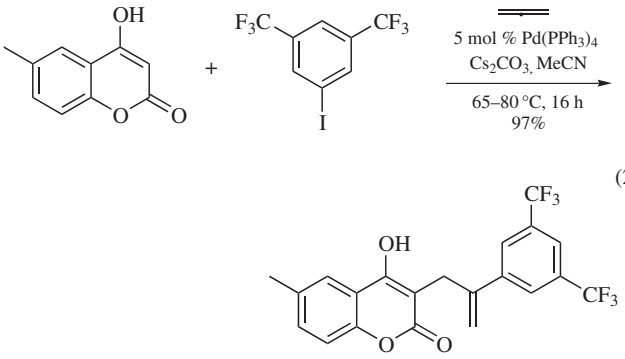
Allylations. 3,5-Bis(trifluoromethyl)iodobenzene has been applied as the aryl iodide component in a Pd(0)-catalyzed three–five–component cascade.[1] An aryl iodide, allene, and heterocyclic pronucleophile components such as 3-phenyl-5-isoxazolone are used in the preparation of 2-arylallyl derivatives in moderate yield (eq 1). *N,N*′-Dimethyl barbiturates can also be synthesized in excellent yields by this palladium-catalyzed cascade. The regioselective addition of palladium–aryl or vinyl halide complex to allenes occurs at the center C-atom furnishing π-allyl species.[2] Only in the presence of an aryl/vinyl halide/triflate can there be the desired Pd(0)-catalyzed reaction resulting in the C2-arylallylation of the active methylene heterocycles. Substituted allenes do not readily participate in this sequence, and in the absence of a nucleophile, β-hydride elimination occurs resulting in 1,3-dienes. When appropriate five- and six-membered heterocycles and aryl/vinyl halide/triflates are used, a wide range of complex allyl substituents can be synthesized, which have proven to be useful scaffolds for drug discovery and combinatorial chemistry.





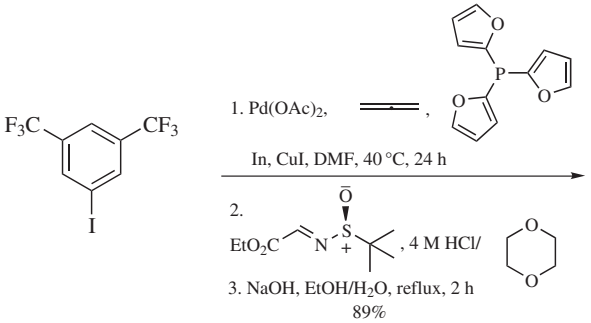
(1)

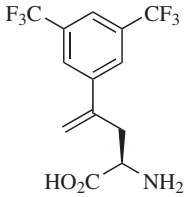
3-Allylation of 4-hydroxycoumarin with 3,5-bis(trifluoromethyl)iodobenzene though a Pd-catalyzed three-component cascade has been reported by Grigg et al. (eq 2).[3] The use of heterocyclic enols 4-hydroxycoumarins as novel nucleophiles for π-allyl palladium(II) species generated in situ from allene and aryl iodides results in clean monoallylation products.[4] *C*-Allylation products do not undergo cyclization even upon workup in aqueous acidic solution, confirming the considerable carbocation character involved in the cyclization. The presence of an electron-withdrawing group on the aryl iodide suppresses cyclization by destabilizing the intermediate carbocation and allows easy isolation of the monoallylation product.



(2)

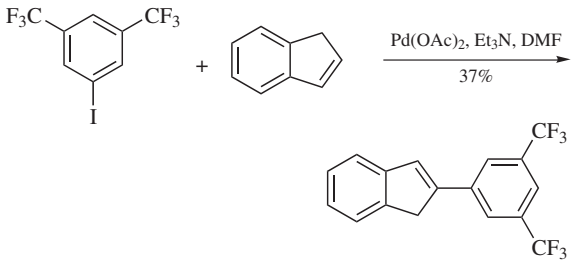
Peptides and proteins containing nonnatural α-amino acids have been applied in the tuning of pharmacokinetics and enhancement of metabolic stability. 3,5-Bis(trifluoromethyl)iodobenzene is utilized to construct these nonproteinogenic amino acids via Pd/In bimetallic catalytic cascade reported by Grigg et al.[5] This process includes the generation of electrophilic π-allyl palladium species, transmetallation to furnish nucleophilic η^1-allyl indium species, allylation of enantiopure *N*-sulfinyl-α-imino esters, and a two-step deprotection (eq 3).





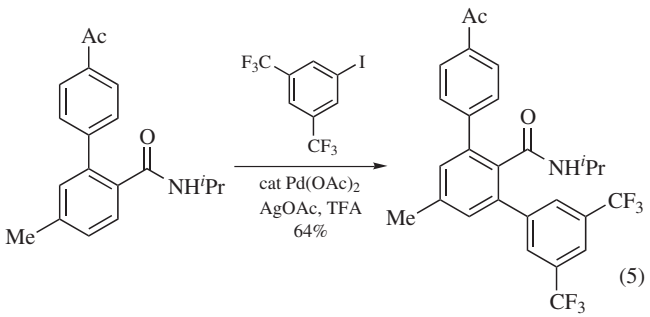
(3)

Arylations. The synthesis of 2-arylindenes though Pd-catalyzed direct arylation of indene with 3,5-bis(trifluoromethyl) iodobenzene has been reported by Nifant'ev et al.[6] 1- and 3-Arylindenes are normally the major products generated via a successive *cis*-addition of aryl-Pd-Hal and *cis*-elimination of H-Pd-Hal.[7] Nevertheless, 2-arylindenes can be synthesized in the presence of palladium acetate with more extensive heating than that required for the typical Heck reaction (eq 4). It has been shown that one of intermediates generated from *cis*-addition of palladium–aryl halide complex may undergo thermal isomerization transforming into a *trans* form followed by *cis*-elimination to furnish 2-arylindenes.



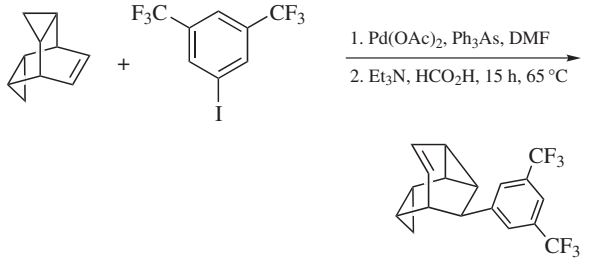
(4)

3,5-Bis(trifluoromethyl)iodobenzene can be used for the direct *ortho*-arylation of benzoic acid amides (eq 5). The palladium-catalyzed reaction proceeds in trifluoroacetic acid and requires the presence of stoichiometric silver acetate.[8] This reaction is an alternative to the *ortho*-lithiation strategies for the synthesis of arylated benzoic acid derivatives that are currently in use. It is also possible to introduce two different aryl groups onto the aromatic ring by sequential arylation. As seen for other catalytic reactions proceeding by a Pd(II)–Pd(IV) mechanism, electron-rich aryl iodides react faster but are more susceptible to side reactions. The reaction also proceeds well with electron-poor aryl iodides. Pyridines, anilines, 8-aminoquinoline benzamides, and benzylamine picolinamides can be arylated by aryl iodides under the Pd(II)–Pd(IV) catalytic cycle conditions.[9]



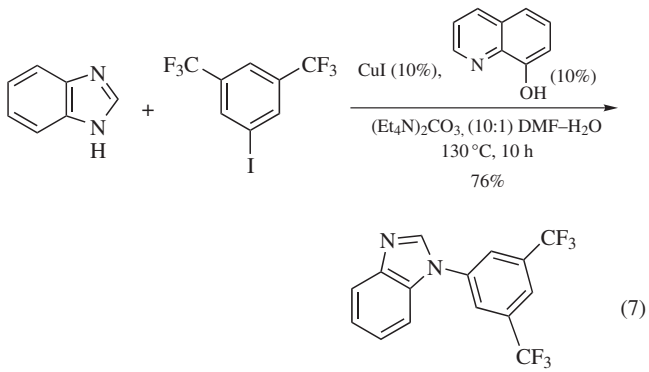
(5)

A π,σ domino-Heck reaction with electron-deficient 3,5-bis(trifluoromethyl)iodobenzene under concomitant rearrangement of tetracyclic allylcyclopropane *endo,exo*-bishomobarrelene has been reported (eq 6).[10,11] This stereoselective reaction proceeds via formation of carbopalladation intermediate, intramolecular insertion into a strained cyclopropane C–C σ-bond, and final *syn*-elimination of hydrido-palladium iodide.



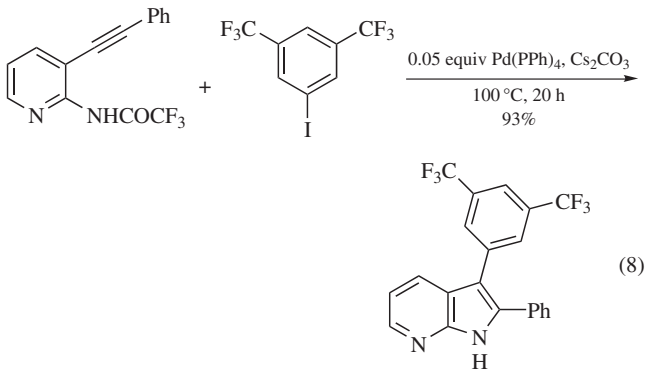
(6)

CuI-catalyzed *N*-arylation of imidazoles with aryl halides has been achieved in a near-homogeneous system that utilizes bis(tetraethylammonium) carbonate (TEAC) as base.[12,13] TEAC, unlike K_2CO_3 or Cs_2CO_3, dissolves in the mixtures, promoting the CuI-catalyzed *N*-arylation of benzimidazoles with aryl halides in DMF. 3,5-Bis(trifluoromethyl)iodobenzene can be converted in over 97% yield after 10 h with TEAC, whereas twice as much time is needed to reach similar conversion with Cs_2CO_3 as base (eq 7). This is the first time an organic carbonate salt has been reported in metal-catalyzed cross-coupling with aryl halides.



(7)

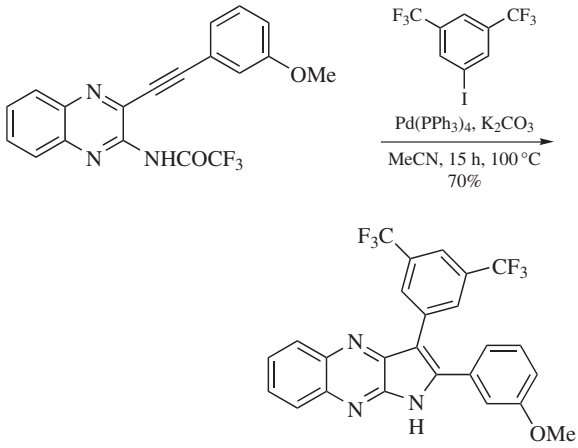
Aminopalladation-reductive Eliminations. Like other aryl iodides, 3,5-bis(trifluoromethyl)iodobenzene has been used in the synthesis of free N–H 2,3-disubstituted azaindoles via an aminopalladation-reductive elimination procedure.[14,15] This procedure is a quite general and versatile tool for synthesizing functionalized indoles and is particularly suited for introducing diversities in the pyrrole ring incorporated into the azaindole system (eq 8).



(8)

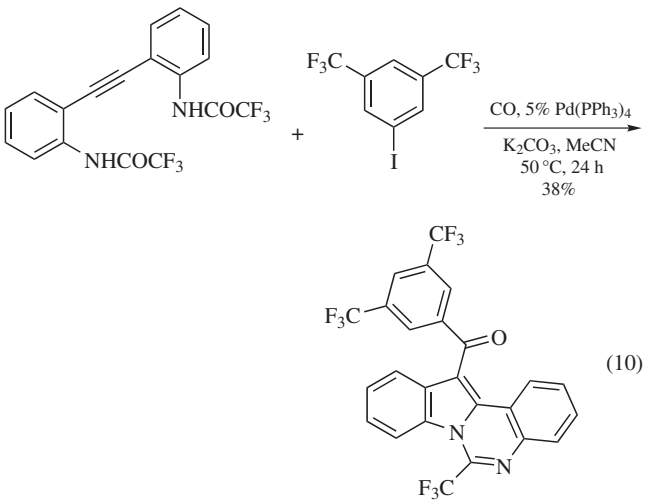
3,5-Bis(trifluoromethyl)iodobenzene is also applied in the synthesis of drug-like products bearing quinoxaline nuclei, which are present in many pharmaceutical agents exhibiting a variety of

bioactivities.[16] 2,3-Disubstituted pyrrolo[2,3-*b*] quinoxaline containing a 3,5-bis(trifluoromethyl)phenyl moiety can be synthesized via an aminopalladation-reductive elimination procedure in 70% yield (eq 9).[17]



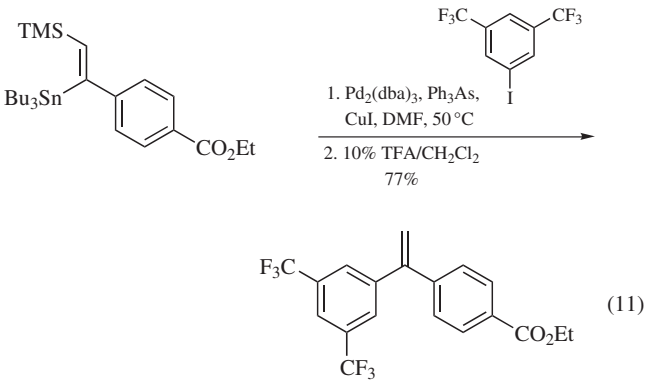
(9)

Cyclocarbonylations. 3,5-Bis(trifluoromethyl)iodobenzene employed in the formation of indoloquinazoline via Pd-catalyzed cyclocarbonylation has been realized (eq 10).[18] Studies reveal that the formation of indoloquinazoline involves several key steps such as aminopalladation-reductive elimination domino reaction, formation of a tetracyclic intermediate via intramolecular nucleophilic attack, and subsequent elimination of a carboxylic acid.[19,20] Due to the strong electron-withdrawing substituents in the aryl iodide, higher carbon monoxide pressure is necessary to increase the yield of the desired product. However, the use of an excessive pressure of carbon monoxide gives low yields of indoloquinazoline.



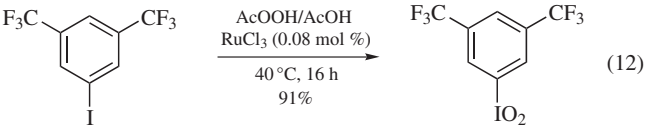
(10)

Stille Coupling Reactions. 3,5-Bis(trifluoromethyl)iodobenzene has been applied in the synthesis of 1,1-diarylethylenes through a combination of Stille coupling with an α-stannyl β-silylstyrene and desilylation under acidic conditions (eq 11).[21] This approach avoids the problematic *cine*-substitution, a well-documented side reaction during the palladium-assisted elaboration of α-substituted vinylstannanes to 1,1-disubstituted ethylenes.[22,23] During the desilylation, the reaction time is inversely related to the electron density of the incoming aryl substrate. When the incoming aryl moiety is more electron rich, the desilylation takes less time.



(11)

Related Reagents. 3,5-Bis(trifluoromethyl)iodobenzene has been transformed into 1-iodyl-3,5-bis(trifluoromethyl)benzene via $RuCl_3$-mediated oxidation in excellent yields (eq 12). Like other iodylarenes, it serves as a mild and highly selective reagent for the oxidation of alcohols to carbonyl compounds.[24] 3,5-Bis(trifluoromethyl)iodobenzene can also be utilized in the easy, safe, and effective method for the synthesis of [bis(trifluoroacetoxy)iodo] arenes as a chemoselective oxidant under $K_2S_2O_8/CF_3COOH/CH_2Cl_2$ conditions (eq 13). This procedure avoids the use of high temperature and severe reaction conditions. Iodoarenes bearing strong electron-withdrawing groups at the *meta*- and *para*-positions give $ArI(OCOCF_3)_2$ in good yields, but the reaction of 3,5-bis(trifluoromethyl)iodobenzene results in low yields due to its lower reactivity.[25] This method is not applicable for iodoarenes with strong electron-donating groups.



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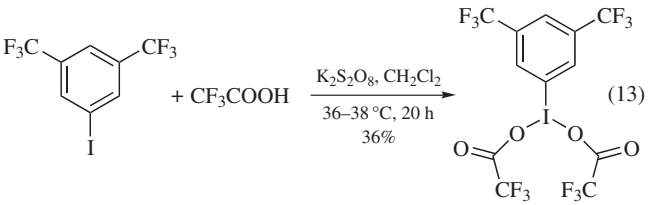
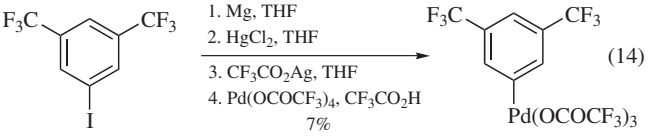


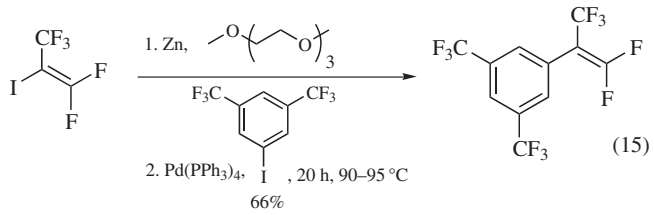
(13)

Like the formation of other aryllead tricarboxylates served as arylating agents, 3,5-bis(trifluoromethyl)phenyllead tristrifluoroacetate has been synthesized using 3,5-bis(trifluoromethyl)-iodobenzene via a similar pathway involving the reaction of arylmercury trifluoroacetate with lead tetrakistrifluoroacetate in trifluoroacetic acid (eq 14).[26]



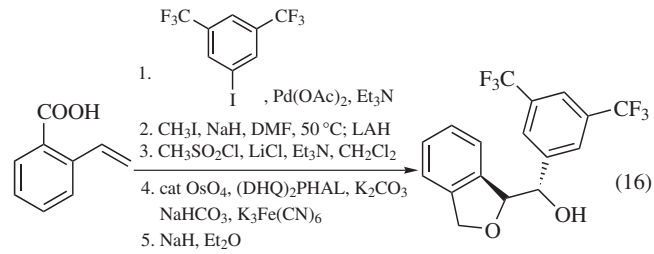
(14)

3,5-Bis(trifluoromethyl)iodobenzene has also been utilized in the synthesis of β,β-difluoro-α-(trifluoromethyl)styrene (DFT) analogs, which are useful building blocks in organofluorine chemistry.[27] Palladium-catalyzed coupling of 3,5-bis(trifluoromethyl)iodobenzene with pentafluoropropen-2-ylzinc reagent can afford the desired styrene in 66% yield (eq 15).



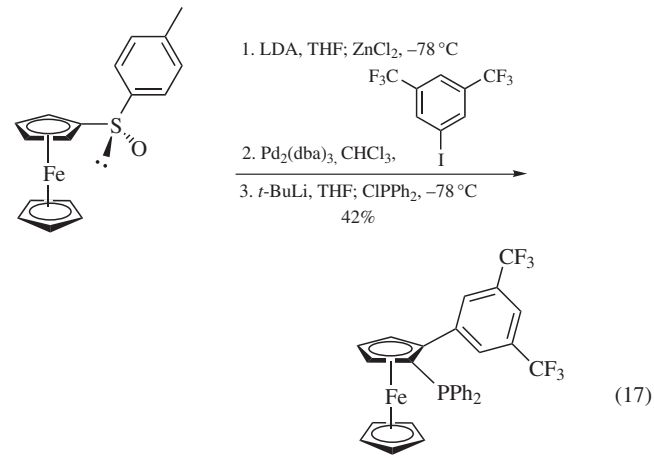
(15)

Like iodobenzene, 3,5-bis(trifluoromethyl)iodobenzene has been employed in the synthesis of chiral β-hydroxy ethers for asymmetric protonation of achiral enolates derived from prochiral ketones (eq 16).[28,29] With the application of the novel chiral reagent possessing 3,5-bis(trifluoromethyl)phenyl functionality, at various temperatures asymmetric protonation of salt-free enolates generated from trimethylsilyl enol ethers provides desired products in good to excellent enantiomeric excess and high yields.



(16)

3,5-Bis(trifluoromethyl)iodobenzene has also been used to develop novel arylmonophosphino ferrocene (MOPF) ligands employed in the field of catalytic asymmetric synthesis.[30,31] Chiral monophosphine ligands are important because of their activity and selectivity in catalytic reactions where the bidendate phosphine-based ligands have failed.[32] The planar chiral 2-aryl-1-diphenylphosphanylferrocene is among the best ligands developed for the palladium-catalyzed asymmetric hydrosilylation of styrene (eq 17). Studies show that aryl groups on the ferrocene scaffold have significant influence on the rate of β-elimination contra the rate of reductive elimination.



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